ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection

Andreone, Pietro ; Colombo, Massimo G ; Enejosa, Jeffrey V ; Koksal, Iftihar ; Ferenci, Peter ; Maieron, Andreas ; Müllhaupt, Beat ; Horsmans, Yves ; Weiland, Ola ; Reesink, Henk W ; Rodrigues Jr., Lino ; Hu, Yiran B ; Podsadecki, Thomas ; Bernstein, Barry

Abstract: BACKGROUND AIMS The interferon-free regimen of ABT-450 (a protease inhibitor), ritonavir, ombitasvir (an NS5A inhibitor), dasabuvir (a non-nucleoside polymerase inhibitor), and ribavirin has shown efficacy in patients with hepatitis C virus (HCV) genotype 1b infection-the most prevalent subgenotype worldwide. We evaluated whether ribavirin is necessary for ABT-450, ritonavir, ombitasvir, and dasabuvir to produce high rates of sustained virologic response (SVR) in these patients. METHODS We performed a multicenter, open-label, phase 3 trial of 179 patients with HCV genotype 1b infection, without cirrhosis, previously treated with peginterferon and ribavirin. Patients were assigned randomly (1:1) to groups given ABT-450, ritonavir, ombitasvir, and dasabuvir, with ribavirin (group 1) or without (group 2) for 12 weeks. The primary end point was SVR 12 weeks after treatment (SVR12). We assessed the noninferiority of this regimen to the rate of response reported (64%) for a similar population treated with telaprevir, peginterferon, and ribavirin. RESULTS Groups 1 and 2 each had high rates of SVR12, which were noninferior to the reported rate of response to the combination of telaprevir, peginterferon, and ribavirin (group 1: 96.6%; 95% confidence interval, 92.8%-100%; and group 2: 100%; 95% confidence interval, 95.9%-100%). The rate of response in group 2 was noninferior to that of group 1. No virologic failure occurred during the study. Two patients (1.1%) discontinued the study owing to adverse events, both in group 1. The most common adverse events in groups 1 and 2 were fatigue (31.9% vs 15.8%) and headache (24.2% vs 23.2%), respectively. Decreases in hemoglobin level to less than the lower limit of normal were more frequent in group 1 (42.0% vs 5.5% in group 2; $P < .001$), although only 2 patients had hemoglobin levels less than 10 g/dL. CONCLUSIONS The interferon-free regimen of ABT-450, ritonavir, ombitasvir, and dasabuvir, with or without ribavirin, produces a high rate of SVR12 in treatment-experienced patients with HCV genotype 1b infection. Both regimens are well tolerated, as shown by the low rate of discontinuations and generally mild adverse events. ClinicalTrials.gov number: NCT01674725.

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~~Interferon-free Combination~~ ABT-450/r/Ombitasvir and Dasabuvir~~Therapy~~ With or Without Ribavirin for Treatment-Experienced ~~Hepatitis~~ HCV~~C~~ Genotype 1b-Infected Patients~~: Results From the PEARL-II Open-Label, Randomised, Phase 3 Trial~~

Short Title: ABT-450/r/Ombitasvir and Dasabuvir for HCV

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Abbreviations: AE, adverse event; DAA, direct-acting antiviral agent; LLN, lower limit of normal; pegIFN, peginterferon; r, ritonavir; RBV, ribavirin; SVR, sustained virologic response; SVR_{12}, sustained virologic response 12 weeks after treatment; TEAE, treatment-emergent adverse event; ULN, upper limit of normal

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Kommentar [DED1]: Title must be 120 characters including spaces
Although it seems our competitors have been allowed more (156 characters below)
Efficacy of an Interferon- and Ribavirin-Free Regimen of Daclatasvir, Asunaprevir, and BMS-791325 in Treatment-Naive Patients With HCV Genotype 1 Infection

Efficacy of Nucleotide Polymerase Inhibitor Sofosbuvir Plus the NS5A Inhibitor Ledipasvir or the NS5B Non-Nucleoside Inhibitor GS-9669 Against HCV Genotype 1 Infection = 167 characters

Kommentar [DED2]: 45 character limit

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~~DISCLOSURES~~Conflicts of Interest:

Pietro Andreone has received ~~:~~ r~~R~~esearch support from Roche, Merck, and Gilead Sciences; served on ~~:~~ A~~a~~dvisory committees for Roche, Merck, Janssen Cilag, AbbVie, Boehringer Ingelheim, Gilead Sciences, and BMS; ~~:~~ and been a c~~C~~onsultant for Merck and BMS.

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Jeffrey V Enejosa, Lino Rodrigues-Jr, Yiran B Hu, Thomas Podsadecki, and Barry Bernstein are~~:~~ e~~E~~mployees of AbbVie and may hold stock or options.

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Author Contributions: PA was the coordinating investigator of the trial, was involved in the study setup, and was responsible for the clinical supervision of patients and performance of the study. MGC, IK, PF, AM, BM, YH, OW, and HWR were investigators in the study, responsible for the treatment of patients and were involved in the acquisition, analysis, and interpretation of the data. YBH performed the statistical analysis and provided input to the analysis plans. ~~LRJ,~~ TP~~,~~ and BB provided scientific input in the clinical study design, reviewed and provided input with regards to the analysis plans. JVE and LRJ were~~was~~ responsible for the conduct and overview of the trial, analysis of the data, and review of the Clinical Study Report. All authors provided critical input and revisions to the writing of the manuscript.

ABSTRACT (~~300~~ 260 word limit, current count ~~297~~260)

Background ~~&~~ Aims: The interferon-free regimen of ABT-450 (protease inhibitor), ritonavir (r), ombitasvir ~~ABT-267~~ (NS5A inhibitor), ~~ABT~~dasabuvir ~~-333~~ (nonnucleoside polymerase inhibitor), and ribavirin (RBV) has shown efficacy in ~~a phase 2 study in~~ patients infected with HCV genotype (GT)1b, the most prevalent subgenotype worldwide. We evaluated whether RBV is necessary with ABT-450/r/~~ABT-267~~ombitasvir, and ~~ABT-333~~dasabuvir to achieve high sustained virologic response (SVR) rates in ~~this population~~GT1b-infected patients.

Methods: PEARL-II was a multicenter, open-label phase 3 trial evaluating 179 ~~treatment~~peginterferon/RBV-experienced, non-cirrhotic HCV GT1b-infected patients randomized 1:1 to ABT-450/r/~~ABT-267~~ombitasvir ~~(150mg/100mg/25mg once daily)~~ and~~,~~ ~~ABT-333~~dasabuvir ~~(250mg twice daily)~~ with ~~weight-based~~ RBV (Group 1_{RBV}) or without (Group 2) for 12 weeks. The primary endpoint was SVR 12 weeks post-treatment (SVR_{12}). Noninferiority to the historical response rate in a similar population treated with telaprevir plus peginterferon/RBV (64%) was assessed.

~~Findings~~Results: High rates of SVR_{12} and non-inferiority to historical rates were achieved ~~whether~~ with (96.6% [95% CI, 92.8–100]) and without RBV ~~was included in the regimen or not (96.6% [95% CI, 92.8 – 100] and~~ 100% [95% CI, 95.9 ~~–~~–100]~~) for Group 1_{RBV} and Group 2, respectively)~~. Additionally, Group 2 was noninferior to Group 1_{RBV}. No virologic failure occurred during the study. Two (1.1%) patients discontinued the study due to adverse events, both in Group 1_{RBV}. The most common adverse events in Groups 1_{RBV} and 2 were fatigue (31.9% vs. 15.8%) and headache (24.2% vs. 23.2%), respectively. Hemoglobin decreases to below the lower limit of normal were ~~statistically~~ more frequent in Group 1_{RBV} (42.0% vs. 5.5%, P <~~0~~.001), although only two patients experienced hemoglobin <~~declines to below~~ 10 g/dL.

Conclusions: The IFN-free regimen of ABT-450/r/~~ABT-267~~ombitasvir, and ~~ABT-333~~dasabuvir, with or without RBV, achieved high SVR_{12} rates in HCV GT1b-infected treatment-experienced patients. Both regimens were well tolerated, ~~as~~ evidenced by the low rate of discontinuations and generally mild adverse events.

~~**Funding:** AbbVie; ClinicalTrials.gov number, NCT01674725~~

Keywords: ~~HCV~~Ribavirin-free~~,~~; ~~direct-acting antiviral~~interferon experienced~~,~~; interferon-free therapy~~,~~; sustained virologic response

INTRODUCTION

Untreated chronic hepatitis C virus (HCV) infection is a leading cause of liver damage, cirrhosis, and hepatocellular carcinoma.[1] Prevalence of HCV infection is estimated at 3% worldwide and results in approximately 350 000 deaths annually.[2, 3] Genotype 1 accounts for approximately 70% of all HCV infections and subgenotype 1b is most predominant in Europe and Eastern Asia. Approved direct-acting antiviral agents (DAAs), telaprevir, boceprevir, sofosbuvir, and simeprevir, given with peg~~ylated~~ interferon (pegIFN) and ribavirin (RBV) have reported sustained virologic response (SVR) rates of 67% to 89% in HCV genotype 1-infected patients. Response rates with DAA regimens are generally lower in patients who have failed previous pegIFN-containing treatment regimens than in treatment-naïve patients, and noticeably lower among prior null responders.[4-8] Additionally, the toxicity of pegIFN and long duration of therapy (up to 48 weeks with some regimens) are a hardship for patients.[9] Notably, pegIFN-based treatment regimens have a well-documented adverse event (AE) profiles including influenza-like symptoms and depression that have led to unfavorable discontinuation rates in clinical trials,[6, 9-12] while RBV also has associated side effects including teratogenicity, hemolytic anemia, and rash.[13, 14]

All-oral and interferon-free HCV treatment regimens with DAAs provide wider treatment access to patients in need with chronic liver disease. ABT-450 is an NS3/4A protease inhibitor with *in vitro* nanomolar antiviral activity and is co-dosed with the CYP3A4 inhibitor, ritonavir (r), which significantly increases peak and trough drug concentrations enabling once-daily dosing.[15] The multi-targeted, all-oral combination of ABT-450/r, ~~ABT-267~~ombitasvir (formerly ABT-267), an HCV NS5A inhibitor with pangenotypic picomolar antiviral activity,[16] and ~~ABT-333~~dasabuvir (formerly ABT-333), an HCV NS5B RNA nonnucleoside polymerase inhibitor, with RBV has shown in a phase 2b trial to achieve high rates of sustained virologic response 12 weeks post-treatment (SVR_{12}) in treatment-naïve and -experienced

genotype 1-infected patients. With this regimen, a 93% SVR_{12} rate was achieved in genotype 1-infected non-cirrhotic patients with prior null response to pegIFN/RBV, and 100% SVR_{12} in the genotype 1b patient subset.[17] These high response rates in prior null responders, considered difficult to treat, are promising and require confirmation in a large phase 3 trial. While ABT-450/r/~~ABT267~~ ombitasvir and ~~ABT-333~~dasabuvir with RBV may achieve high SVR_{12} rates, determining the benefit gained by including RBV in the regimen has not been assessed in these patients. This phase 3 study (PEARL-II) evaluated the efficacy and safety of 12-week treatment with ABT-450/r/~~ABT267~~ ombitasvir~~+~~ and ~~ABT-333~~dasabuvir with or without RBV exclusively in non-cirrhotic pegIFN/RBV treatment-experienced HCV genotype 1b-infected patients.

METHODS

Patients. Adults were 18 to 70 years old at the time of screening from 43 sites in Austria, Belgium, Italy, The Netherlands, Portugal, Puerto Rico, Sweden, Switzerland, Turkey, and the United States. Patients were required to have documentation that they previously failed treatment with pegIFN/RBV. Eligible patients were required to be non-cirrhotic with chronic HCV genotype 1b-infection for at least 6 months with an HCV RNA level > 10 000 IU/mL at screening. Patients were excluded if they had evidence of co-infection with any HCV genotype other than 1b or tested positive for Hepatitis B surface antigen or anti-HIV antibody at screening. Detailed eligibility criteria are provided in the Supplementary Appendix.

Study design. Patients were stratified by type of previous non-response to pegIFN/RBV treatment (null responders, partial responders, and relapsers) and randomized 1:1 to receive the 12-week regimen of ABT-450/r/~~ABT-267~~ombitasvir (150mg/100mg/25mg once daily) and ~~ABT-333~~dasabuvir (250mg twice daily) with either weight-based RBV dosed twice daily (1000mg daily if body weight was less than 75kg, 1200mg daily if body weight was greater than or equal to 75kg) for Group 1_{RBV} or without RBV for Group 2. After 12 weeks of treatment, patients were followed for 48 additional weeks. Additional details on study design are in the Supplementary Appendix.

The study was conducted in accordance with the International Conference of Harmonisation guidelines, applicable regulations, and guidelines governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki (ClinicalTrials.gov number, NCT01674725). All patients provided written informed consent.

Safety Assessments. Adverse event assessments were reported from the time of study drug administration until 30 days after last dose and were judged mild, moderate, or severe; clinical laboratory testing was performed at each study visit. Serious AEs were collected throughout the study.

Efficacy Endpoints. Plasma samples were collected at screening and each study visit and HCV RNA levels determined using the Roche COBAS TaqMan real-time RT-PCR assay v2.0 at a central lab. A fixed-sequence testing procedure was used to control Type I error at 0.05. The primary efficacy endpoint was noninferiority of the SVR_{12} rates (assessed by HCV RNA < 25 IU/mL) of Group 2 and Group 1_{RBV} to the historical SVR_{12} rate for telaprevir plus pegIFN/RBV in HCV genotype 1b-infected patients who were relapsers, partial responders, or null-responders to previous pegIFN/RBV treatment,[4] adjusted for non-cirrhotic patients in this study. Group 1_{RBV} and Group 2 noninferiority could be claimed if the SVR_{12} lower bound of the 95% confidence interval (CI) was greater than the upper bound of the CI for the historical rate minus a 10.5% noninferiority margin (64%). Further details of historical noninferiority calculations are provided in the Supplementary Appendix. Secondary efficacy endpoints in the fixed-sequence included the following: (1) comparison of the percentage of patients with a decrease in hemoglobin to below the lower limit of normal (LLN) at the end of treatment; (2) superiority of Group 1_{RBV} and Group 2 to the historical rate for telaprevir plus pegIFN/RBV (75%); and (3) noninferiority of Group 2 to Group 1_{RBV} using a 10.5% noninferiority margin for the SVR_{12} difference. The percentage of patients with on-treatment virologic failure and post-treatment relapse was also assessed.

Virologic failure criteria. Virologic failure leading to discontinuation of study drug was determined if the following criteria occurred: confirmed increase from nadir in HCV RNA (defined as 2 consecutive HCV RNA measurements greater than 1 $\log_{10}$ IU/mL above nadir) at any point during treatment; failure to achieve HCV RNA < 25 IU/mL by Week 6; and confirmed HCV RNA ≥ 25 IU/mL in two consecutive measurements at any point during treatment after HCV RNA < 25 IU/mL. Post-treatment relapse was confirmed in patients with HCV RNA < 25 IU/mL at the end of treatment and subsequent RNA ≥ 25 IU/mL in two consecutive measurements.

Statistical Analyses. Efficacy analyses were performed using the intent-to-treat population defined as all randomized HCV genotype 1b-infected patients who received at least one dose of coformulated ABT-450/r/~~ABT-267~~ombitasvir. The safety population included all patients that received at least one dose of study drug. A population of 90 patients per treatment arm was calculated to provide greater than 90% power to achieve noninferiority of the active regimen to the historical threshold (64%).

SAS software for the UNIX operating system was used for all analyses. All statistical tests and all confidence intervals were two-sided with a significance level of 0.05.

RESULTS

Baseline Patient Demographics and Characteristics. Patient screening began 14 August 2012 and the last SVR_{12} data were collected 16 January 2014. Of 324 patients screened, 187 were randomized and 186 received study drug (91 Group 1_{RBV}, 95 Group 2) (Figure 1). Null-responders, partial-responders, and relapsers to previous pegIFN/RBV treatment made up 34.9%, 28.5%, and 36.6% of the study population, respectively, evenly stratified between treatment arms (Table 1). Reasons for screen failures are provided in the Supplemental Appendix. Seven randomized patients, three in Group 1_{RBV} and four in Group 2 were not included in the intent-to-treat efficacy population. Of these, six patients were enrolled prior to a protocol amendment and received non-coformulated ABT-450/r/~~ABT-267~~ombitasvir, 3 of whom were genotype 1a; a seventh patient's HCV subgenotype was not determined.

Efficacy. After 12 weeks of treatment, 96.6% (85/88; 95% CI, 92.8 – 100) of Group 1_{RBV} and 100% (91/91; 95% CI, 95.9 – 100) of Group 2 patients achieved SVR_{12} using the intent-to-treat population for both groups (Table 2). For the primary endpoint, SVR_{12} rates in both treatment groups were noninferior to the historical SVR rate for telaprevir plus pegIFN/RBV in comparable treatment-experienced patients. Both treatment groups were also superior to the historical rate. Noninferiority of Group 2 to Group 1_{RBV} was met as the treatment difference in SVR_{12} rates was 3.4% (95% CI, -0.4 – 7.2).

No patients from either treatment group experienced on-treatment virologic failure or post-treatment relapse. Of the three patients in Group 1_{RBV} that did not achieve SVR_{12}, two (2.3%) patients discontinued study drug due to AEs, and one patient was lost to follow-up after SVR_4 (Table 3).

Sustained virologic responses in both groups were not influenced by previous non-response, age, race, or IL28B genotype. Among Group 1_{RBV} null-responders, partial-responders, and relapsers to previous pegIFN/RBV treatment, SVR_{12} rates were 93.5%, 96.0%, and 100%, respectively. Group 1_{RBV} rates were

similarly high regardless of IL28B genotype (CC: 100%, CT: 96.4%, TT: 95.5%), or sex (male: 95.3%, female: 97.8%). Group 2 SVR_{12} rates were 100% in all subgroups.

Lastly, the seven patients excluded from the efficacy subset due to receiving non-coformulated study drug, confirmed genotype 1a, or undetermined genotype all completed treatment and achieved SVR_{12}.

Safety. Treatment-emergent AEs (TEAE) were experienced by 79.1% of patients in Group 1_{RBV} and 77.9% of patients in Group 2. Most TEAEs were mild with the most commonly reported events in Group 1_{RBV} and Group 2 being fatigue (31.9% vs. 15.8%, P = ~~0~~.015), headache (24.2% vs. 23.2%, P = NS~~> 0.05~~), and nausea (20.9% vs. 6.3%, P = ~~0~~.005), respectively (Table 3). Patients in Group 1_{RBV} also experienced statistically significantly more events of insomnia, anemia, rash, and increased blood bilirubin, all known to be associated with RBV use; no patient discontinued study drug due to these events.

Overall, two (1.1%) patients discontinued treatment due to AEs, both in Group 1_{RBV}. One patient experienced two serious AEs of pancreatitis that were considered by the investigator not to be study drug related. This patient had elevated amylase on Day 1 prior to receiving study drug; on Day 11, the patient reported abdominal pain and was hospitalized on Day 13, at which point study drugs were discontinued. The patient experienced another mild episode of pancreatitis on Day 31 that resolved by Day 36. Another patient reported anxiety, tachycardia, fever, and dyspnea on Day 36 that led to study discontinuation. Three other serious TEAEs included cellulitis, nephrolithiasis, and osteoarthritis; none were judged to be study drug-related.

Hemoglobin levels below the LLN at end of treatment, a secondary endpoint, was experienced more often by patients in Group 1_{RBV} compared to Group 2 (42.0% vs. 5.5%, respectively, P < ~~0~~.001), although clinically significant grade 2 hemoglobin declines to below 10 g/dL at the end of treatment occurred in only 2 (1.1%) of patients, both in Group 1_{RBV}. No patient required a blood transfusion or erythropoietin. Elevations in total bilirubin greater than 2 x the upper limit of normal (ULN) were reported in 15.4% of

patients in Group 1_{RBV} and 1.1% of patients in Group 2 ($P < ~~0~~.001$), with 8.8% of patients in Group 1_{RBV} and 0% in Group 2 reporting greater than 3 x ULN. Mean levels of bilirubin were elevated at Week 1 in both groups, but bilirubin levels (predominantly indirect bilirubin) remained elevated throughout the treatment period only in Group 1_{RBV} (Supplemental Figure S3). Five (5.5%) patients in Group 1_{RBV} and 2 (2.1%) patients in Group 2 reported hyperbilirubinaemia; three (3.3%) patients in Group 1_{RBV} reported jaundice. One hyperbilirubinaemia and one jaundice event were moderate in severity and the remaining events were judged mild; none led to study drug discontinuation. Ribavirin dose modification occurred in five patients, three due to anemia, one due to hyperbilirubinaemia, and one was dose adjusted due to decrease in weight; all achieved SVR_{12}.

The percentage of patients with post-baseline alanine aminotransferase (ALT) levels greater than 3 x ULN was similarly low for both treatment groups. No patient experienced post-baseline ALT level greater than 5 x ULN. One patient in Group 2 had an aspartate aminotransferase (AST) level greater than 5 x ULN at a single time study visit, with all subsequent values normal. Twelve weeks of treatment with these regimens normalized liver enzymes in almost all patients with elevated baseline liver enzymes: 96.9% (63/65) and 100% (66/66) of Group 1_{RBV} and Group 2 patients, respectively, with high baseline ALT levels reached normal values following treatment; AST levels were normalized in 98.4% (60/61) and 91.8% (56/61) of Group 1_{RBV} and Group 2 patients, respectively. Median changes from baseline in aminotransferase values at final treatment visit were similar comparing treatment groups (ALT: -35.0 vs. -36.0 U/L; AST: -22.0 vs. -21.0 U/L for Group 1_{RBV} and Group 2, respectively).

DISCUSSION

PEARL-II examined an all-oral, interferon-free regimen with or without RBV exclusively in pegIFN/RBV treatment-experienced, non-cirrhotic patients with HCV genotype 1b infection. The intent-to-treat SVR_{12} rates of 96.6% to 100% in patients receiving the 12-week regimen of ABT-450/r/~~ABT-267~~ombitasvir and ~~ABT-333~~dasabuvir with or without RBV, respectively, were superior to the historical rate of telaprevir plus pegIFN/RBV. The SVR_{12} rates of this multi-targeted regimen with RBV confirm results of the Phase 2b AVIATOR study[17] in prior null-responders, the most difficult to treat of pegIFN/RBV non-responders, and further expands efficacy conclusions to patients who were partial responders and relapsers to pegIFN/RBV treatment. In addition, PEARL-II demonstrated noninferiority of the RBV-free regimen to the RBV-containing regimen, supporting the use of ABT-450/r/~~ABT-267~~ombitasvir and ~~ABT-333~~dasabuvir without RBV for 12 weeks in the treatment of HCV genotype 1b-infected pegIFN/RBV-experienced patients without cirrhosis.

The TEAEs associated with either group in this 12-week regimen were generally mild and manageable. Overall, only two (1.1%) treated patients discontinued treatment due to AEs, and the five serious TEAEs reported in four patients were considered to be unrelated to study drug by the investigators. As expected, known RBV adverse events (fatigue, nausea, insomnia, rash, anemia, and increased bilirubin) were statistically more prevalent in $Group1_{RBV}$, although frequency and severity appear reduced compared to when RBV is combined with pegIFN.[7, 18] Hemoglobin declines were also more frequent in Group 1_{RBV} although few (2.2%) reached clinical significance, and AEs leading to RBV dose reduction occurred in only four patients. Elevated bilirubin levels in Group 1_{RBV} were predominantly due to indirect bilirubinemia, consistent with the hemolysis associated with RBV and the known effect of ABT-450 on the bilirubin transporter OATP1B1, though lack of bilirubin elevations in Group 2 suggest the

predominant cause was RBV-related hemolysis. Liver enzyme normalization was consistent with the high rate of virologic response.

The SVR_{12} rates reported here compare favorably to published reports of other interferon-free regimens using the NS5B RNA polymerase inhibitor sofosbuvir in combination with NS5A inhibitors (daclatasvir or ledipasvir), or with an NS3/4A protease inhibitor (simeprevir). Combinations of sofosbuvir plus daclatasvir with or without RBV have shown greater than or equal to 95% SVR_{12} in 41 treatment-experienced genotype 1 patients, of which only eight patients were genotype 1b.[19] Similar SVR_{12} rates have been reported in treatment-experienced genotype 1 patients with sofosbuvir plus ledipasvir with (21/21, 100%) or without RBV (18/19, 95%), although only six genotype 1b patients were included.[20] In 13 genotype 1b-infected patients receiving the combination of simeprevir plus sofosbuvir with or without RBV, 100% SVR_8 was reported.[21] Together with the results from PEARL-II, these data support a multi-targeted approach to achieve SVR; however, no other studies have exclusively analyzed, nor had the statistical power to draw conclusions regarding efficacy, including the contribution of RBV, in treatment-experienced HCV genotype 1b patients as the PEARL-II study does.

One of the strengths of the PEARL-II study includes its large sample size in genotype 1b-infected patients, the most prevalent subgenotype worldwide, including patients with previous null response and relapse to pegIFN/RBV treatment. Treatment-experienced genotype 1b-infected patients have not been extensively studied with currently approved or investigational IFN-free regimens, hence this large patient population represents a group with unmet need. Study limitations include the open label study design, the exclusion of patients with cirrhosis, HBV or HIV coinfection, and that these findings may be specific to genotype 1b-infected patients. However, this regimen is also being investigated in parallel phase 3 studies in treatment-naïve patients infected with genotype 1a and 1b, and in patients with cirrhosis.

In conclusion, a 12-week regimen of ABT 450/r/~~ABT-267~~ombitasvir and ~~ABT-333~~dasabuvir with or without RBV was generally well-tolerated in pegIFN/RBV treatment experienced, non-cirrhotic, HCV genotype 1b-infected adults, as evidenced by the low rate of treatment discontinuation and serious adverse events. Additionally, the regimen without RBV was associated with fewer adverse events of fatigue, nausea, insomnia, rash, and a lower rate of laboratory abnormalities including bilirubin elevation and hemoglobin decrease. Sustained virologic response rates of 96.6% and 100% were achieved, including 93.5% and 100% in the difficult to treat previous pegIFN/RBV null-responders, with or without RBV, respectively. Therefore, ABT-450/r/~~ABT-267~~ombitasvir and ~~ABT-333~~dasabuvir without RBV is ~~recommended~~ sufficient to achieve optimal treatment efficacy~~for treatment~~ of HCV genotype 1b infection in this population.

~~*Panel.*~~

~~**Research in context**~~

~~**SYSTEMATIC REVIEW**~~

~~In February 2014, we used Pubmed with the search "HCV" AND "Null responder", which produced 12 results. Among the results was a literature review published in 2013 highlighting the trial data of currently approved or investigative DAAs with or without peg/IFN.[22] The literature review included data from seven protease inhibitors, three nucleoside inhibitors, four nonnucleoside inhibitors, and three NS5A inhibitors.~~

~~**INTERPRETATION**~~

~~Focusing specifically on the population investigated in PEARL-II, of the 11 cited studies (excluding publications with the regimen presented here), four included non-cirrhotic, treatment-experienced genotype 1-infected patients, and only three exclusively examined subgenotype 1b. In the four genotype 1 studies, the sum of the patient population examined was 80; however, the sum of genotype 1b patients examined was only 38. Sustained virologic response rates in these patients were 83% (15/18) to 100% (2/2) using asunaprevir plus pegIFN and daclatasvir[23-25]. The combination of sofosbuvir plus daclatasvir with or without RBV achieved SVR_{12} in 100% (8/8) genotype 1b-infected patients.[19] Importantly, all of these studies were with 24 weeks of treatment compared to the 12-week regimen we present. Additionally, only eight prior null responders with genotype 1b infection were receiving pegIFN-free therapies. In comparison, the PEARL-II study was powered to specifically examine genotype 1b prior non-responders to pegIFN/RBV treatment with a multi-targeted 12-week treatment. Individual HCV treatment regimens vary in their efficacy to different genotypes, thus critically analysing each as we have done is of significant importance. The efficacy population of the PEARL-II study (N = 179) robustly~~

~~supports the SVR conclusions in this under-studied genotype 1b population that represents the most prevalent HCV infection worldwide.~~

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~~**DISCLOSURES**~~

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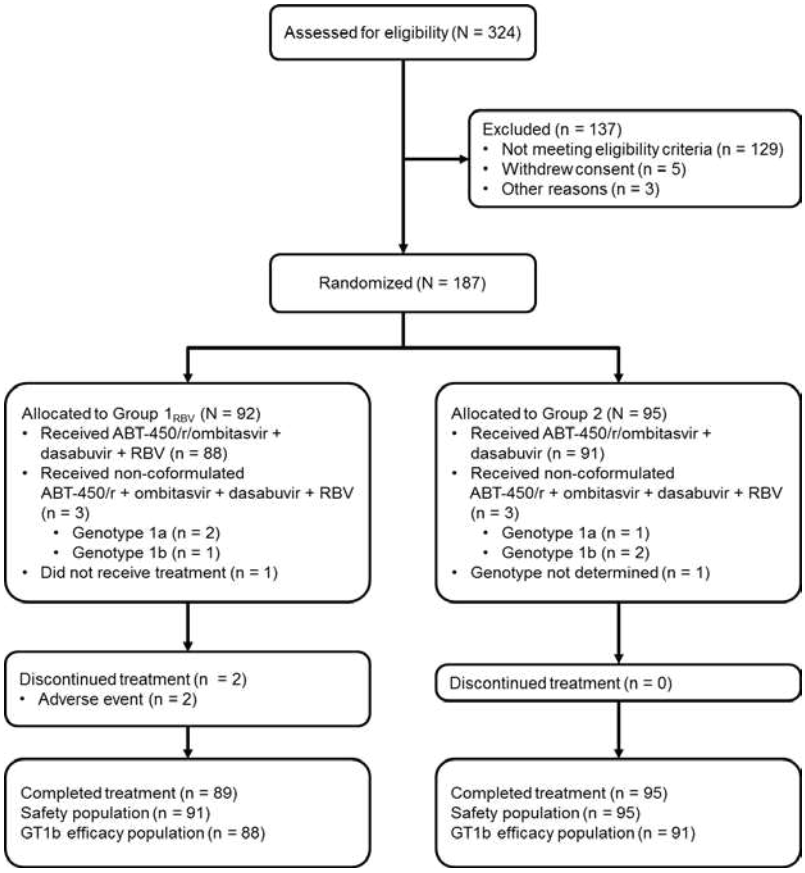

Figure 1. Patient flow diagram.

Table 1. Baseline demographics and characteristics, n (%)

Parameter	Group 1_{RBV} 3-DAA + RBV (N = 91)	Group 2 3-DAA (N = 95)
Sex, male	45 (49.5)	57 (60.0)
Race		
White	84 (92.3)	86 (90.5)
Black	3 (3.3)	6 (6.3)
Ethnicity, Hispanic/Latino	4 (4.4)	2 (2.1)
Geographic region		
North America	14 (15.4)	19 (20.0)
Europe	77 (84.6)	76 (80.0)
Age (years), mean (±SD)	54.2 ± 10.9	54.2 ± 10.5
BMI (kg/m^2), mean (±SD)	26.2 ± 4.1	27.5 ± 4.3
IL28B genotype		
CC	10 (11.0)	7 (7.4)
Non-CC	81 (89.0)	88 (92.6)
HCV RNA (log_{10} IU/mL), mean (±SD)	6.56 ± 0.56	6.48 ± 0.53
Previous pegIFN/RBV non-response		
Null responder	32 (35.2)	33 (34.7)
Partial-responder	26 (28.6)	27 (28.4)
Relapser	33 (36.3)	35 (36.8)
Baseline fibrosis stage		
F0 – F1	64 (70.3)	61 (64.2)

F2	13 (14.3)	21 (22.1)
F3	14 (15.4)	13 (13.7)

Fibrosis scoring information is provided in the Supplemental Appendix. BMI, body mass index; pegIFN, peg~~ylated~~ interferon; RBV, ribavirin.

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Table 2. Intent-to-treat[a] virologic response, n/N (%)

Parameter	Group 1_{RBV} 3-DAA + RBV	Group 2 3-DAA	Treatment difference (95% CI)
SVR_{12}	85/88 (96.6)	91/91 (100)	3.4 (-0.4, 7.2)
Previous non-response			
Null responder	29/31 (93.5)	32/32 (100)	6.5 (-2.2, 15.1)
Non/partial responder	24/25 (96.0)	26/26 (100)	4.0 (-3.7, 11.7)
Relapser	32/32 (100)	33/33 (100)	0 (N/A)
Sex			
Male	41/43 (95.3)	54/54 (100)	4.7 (-1.6, 10.9)
Female	44/45 (97.8)	37/37 (100)	2.2 (-2.1, 6.5)
Race			
Black	3/3 (100)	5/5 (100)	0 (N/A)
Non-black	82/85 (96.5)	86/86 (100)	3.5 (-0.4, 7.5)
IL28B genotype			
CC	10/10 (100)	7/7 (100)	0 (N/A)
CT	54/56 (96.4)	64/64 (100)	3.6 (-1.3, 8.4)
TT	21/22 (95.5)	20/20 (100)	4.5 (-4.2, 13.2)

[a]Intent-to-treat genotype 1b efficacy population includes all patients with subgenotype 1b infection who were assigned to and treated with ABT-450/r/~~ABT-267~~ombitasvir co-formulated drug.

DAA, direct acting antiviral; RBV, ribavirin; SVR_{12}, 12-week sustained virologic response.

Table 3. Patients Reporting TEAEs, n (%)

Parameter	Group 1_{RBV} 3-DAA + RBV (N = 91)	Group 2 3-DAA (N = 95)	*P* value
Any TEAE	72 (79.1)	74 (77.9)	
Any severe TEAE	0 (0)	1 (1.1)	
Any serious TEAE	2 (2.2)	2 (2.1)	
TEAE leading to discontinuation	2 (2.2)	0 (0)	
Common TEAEs[a]			
Fatigue	29 (31.9)	15 (15.8)	0.015
Headache	22 (24.2)	22 (23.2)	
Nausea	19 (20.9)	6 (6.3)	0.005
Insomnia	13 (14.3)	3 (3.2)	0.008
Pruritus	13 (14.3)	8 (8.4)	
Diarrhea	12 (13.2)	12 (12.6)	
Asthenia	11 (12.1)	7 (7.4)	
Anemia	10 (11.0)	0 (0)	< 0.001
Blood bilirubin increased	8 (8.8)	0 (0)	0.003
Rash	8 (8.8)	1 (1.1)	0.017
Chemistry and Hematologic values of interest during treatment			
Hemoglobin below LLN at end of treatment[b]	37 (42.0)	5 (5.5)	< 0.001
Total bilirubin > 3X ULN	8 (8.8)	0 (0)	0.003
ALT > 5X ULN	0 (0)	0 (0)	
AST > 5X ULN	0 (0)	1 (1.1)	

[a]Investigator-reported TEAEs present in ≥ 10 % of either treatment group or with a statistically significant difference between treatment groups.

[b]N's = 88 and 91 for Group 1_{RBV} and Group 2, respectively, using the intent-to-treat genotype 1b efficacy population.

TEAE, treatment-emergent adverse event; DAA, direct acting antiviral; RBV, ribavirin; LLN, lower limit of normal; ULN, upper limit of normal; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

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